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# Faecal haemoglobin can define risk of colorectal neoplasia at surveillance colonoscopy in patients at increased risk of colorectal cancer.

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## Abstract

**Background:** Quantitative faecal immunochemical tests measure faecal haemoglobin concentration (f-Hb), which increases in the presence of colorectal neoplasia.

**Objective:** We examined the diagnostic accuracy of faecal immunochemical test (FIT) in patients at increased risk of colorectal cancer (CRC) attending for surveillance colonoscopy as per national guidelines.

**Methods:** A total of 1103 consecutive patients were prospectively invited to complete a FIT before their scheduled colonoscopy in two university hospitals in 2014–2016. F-Hb was analysed on an OC-Sensor io automated analyser (Eiken Chemical Co., Ltd, Tokyo, Japan) with a limit of detection of 2 µg Hb/g faeces. The diagnostic accuracy of f-Hb for CRC and higher-risk adenoma was examined.

**Results:** A total of 643 patients returned a faecal test. After excluding 4 patients with known inflammatory bowel disease, 639 (57.9%) remained in the study: age range: 25–90 years (median: 64 years, interquartile range (IQR): 55–71): 54.6% male. Of 593 patients who also completed colonoscopy, 41 (6.9%) had advanced neoplasia (4 CRC, 37 higher-risk adenoma). Of the 238 patients (40.1%) who had detectable f-Hb, 31 (13.0%) had advanced neoplasia (2 CRC, 29 higher-risk adenoma) compared with 10 (2.8%) in those with undetectable f-Hb (2 CRC, 8 higher-risk adenoma). Detectable f-Hb gave negative predictive values of 99.4% for CRC and 97.2% for CRC plus higher-risk adenoma.

**Conclusion:** In patients at increased risk of CRC under colonoscopy surveillance, a test measuring faecal haemoglobin can provide an objective estimate of the risk of advanced neoplasia, and could enable tailored scheduling of colonoscopy.

## Keywords

Adenoma, colorectal neoplasms, faecal immunochemical test, faecal haemoglobin, colonoscopy, surveillance

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## Key Summary

### *The established knowledge on this subject*

- Quantification of faecal haemoglobin concentration (f-Hb) using a Faecal Immunochemical Test (FIT) is advocated for population bowel screening and as a ‘rule-out’ test within the assessment of new bowel symptoms presenting to family doctors.

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- A variety of f-Hb have been selected as the cut-off for a 'positive' test in diagnostic accuracy studies published to date.
- Few studies have examined the role of FIT in patients under regular surveillance colonoscopy.

### *The significant and new findings of this study*

- We describe using FIT at the limit of detection (LoD), prior to scheduled surveillance colonoscopy in a cohort of patients at increased risk of colorectal cancer (CRC).
- With a positive FIT, prevalence of advanced neoplasia was doubled, and with a negative FIT it was reduced by 60%.
- FIT provides objective evidence of the risk of advanced neoplasia at pending surveillance colonoscopy and could inform patient-centred colonoscopy scheduling.

## Introduction

Early diagnosis of colorectal cancer (CRC) is associated with improved outcomes,<sup>1</sup> and removal of colorectal adenoma can prevent the subsequent development of CRC.<sup>2</sup> Unfortunately, because any symptoms associated with CRC are extremely non-specific and, alone, show poor diagnostic performance,<sup>3,4</sup> and because adenomas are generally asymptomatic, individuals who are at moderate or high risk of developing CRC are recommended to undergo regular surveillance colonoscopy. The British Society of Gastroenterology (BSG) guidelines for Colorectal Cancer Screening and Surveillance provide the benchmark for practice in the United Kingdom (UK).<sup>5</sup> Individuals are recommended to undergo colonoscopy at specified intervals according to their individual risk profile. However, precise surveillance intervals have, to date, been defined solely by expert opinion. Furthermore, the yield of pathology at surveillance colonoscopy is low: for example, only a 1.8% incidence of CRC in almost 12,000 patients in one study.<sup>6</sup> Surveillance colonoscopy is viewed as the gold standard investigation, but it has a miss rate of 11% for advanced adenoma, and up to 26% for all adenoma,<sup>7,8</sup> is associated with an interval cancer rate of 0.6% in patients under surveillance,<sup>9</sup> and carries a small but significant risk of complication such as perforation of the bowel. A better means of surveillance that can triage individuals for colonoscopy at the appropriate time is urgently required.

Faecal immunochemical tests for haemoglobin (FIT) measure faecal haemoglobin concentrations (f-Hb), which are correlated directly with the severity of any underlying neoplastic colorectal lesions.<sup>10</sup> These are widely used in CRC screening and are now advocated for use in primary care, along with clinical and laboratory data, as a 'rule-out' test in the assessment of patients presenting with new bowel symptoms and thus avoid unnecessary colonoscopy.<sup>11–15</sup> FIT has been advocated for the screening of first-degree relatives of CRC patients,<sup>16</sup> and has shown equivalence to colonoscopy in familial CRC screening.<sup>17</sup> A number of studies

have examined the utility of FIT within patients under colonoscopy surveillance, reporting on qualitative and quantitative assays and suggesting high specificity and negative predictive values for CRC at low f-Hb cut-offs.<sup>18–21</sup> More recently, a study reported less favourable results in patient under adenoma surveillance, but this used a higher f-Hb cut-off of 40 µg Hb/g faeces.<sup>22</sup>

There is much current interest in using very low f-Hb in several clinical settings, since the lower the cut-off, the more neoplasia will be detected. Analytical performance at low f-Hb is defined by the detectability characteristics. These can be described as the limit of detection (LoD), below which f-Hb is undetectable, and above which f-Hb is detected; the limit of quantitation (LoQ), above which the f-Hb is quantifiable in numerical terms; and the working range, which is analyser dependent and determines the f-Hb that is reported in practice.<sup>23</sup> We aimed to determine the diagnostic accuracy of a quantitative FIT at low f-Hb for advanced neoplasia (CRC plus higher-risk adenoma (HRA)) at the time of scheduled colonoscopy in individuals at increased risk of CRC and engaged in a surveillance programme, whether it was feasible and acceptable to patients, and whether it could be used to tailor surveillance colonoscopy for individual patients.

## Methods

This prospective study was conducted following the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.<sup>24</sup> Consecutive patients at risk of CRC, as defined by the BSG guidelines for Colorectal Cancer Screening and Surveillance (2010 edition),<sup>5</sup> and enrolled in colonoscopy surveillance at Ninewells Hospital and Medical School, Dundee from 1 June 2014, for a period of 15 months, and at St Marks Hospital, London from 1 June 2016, for a period of 3 months, were eligible. Patients with inflammatory bowel disease (IBD) were excluded. Data collection concluded on 30 September 2016.

Individuals were identified from endoscopy surveillance registers and were contacted in date order as their appointment time approached by a nurse specialist who booked a surveillance colonoscopy, provided the patient still fulfilled the surveillance criteria described by the BSG guidelines.<sup>5</sup> The nurse invited each patient to submit a single sample of faeces for FIT analysis prior to colonoscopy. Sample collection for FIT was completed before bowel preparation started. A FIT specimen collection device (OC-Sensor, Eiken Chemical Co., Ltd, Tokyo, Japan) and a pictorial patient information sheet were sent to the patient's home. Samples were returned to Blood Sciences, NHS (National Health Service) Tayside, and this implied consent to take part in the study. Analysis was performed on an OC-Sensor io automated analyser (Eiken). That analyser provided numerical results from 0 to >200 µg Hb/g faeces, with a manufacturer's stated LoD of 2 µg Hb/g faeces and LoQ of 4 µg Hb/g faeces: 10–200 µg Hb/g faeces is conventionally taken as the working range. Analysis was performed in advance of colonoscopy in all cases. Feasibility and acceptability of application of FIT was measured by uptake. Colonoscopy was performed within 4 weeks of the FIT test. Patient symptoms were not recorded. Endoscopists were blind to the f-Hb result and recorded colonoscopy findings on the hospitals' electronic endoscopy reporting systems. Polyp size and number were verified by a specialist gastrointestinal pathologist. Adenomatous polyps were grouped by size (<10 mm, ≥10 mm) and number. Individuals with small rectal hyperplastic polyps were considered as normal. If multiple lesions were present, classification was based on the most advanced lesion. HRA was defined as at least three adenoma or any ≥10 mm.

Results of f-Hb analysis were correlated with colonoscopy and pathology findings. Using the pre-specified analyser and working range thresholds, sensitivity and specificity of f-Hb for detecting CRC and HRA were estimated, in addition to positive predictive values (PPV) and negative predictive values (NPV), expressed with 95% confidence intervals.

Statistical analyses were performed with MedCalc (MedCalc Software, Ostend, Belgium).

## Results

Altogether, 1103 patients were invited, and 643 returned a FIT device (uptake: 58.3%). Of the 790 patients approached in Dundee, 516 enrolled (64.9%), compared with 127 of the 313 invited in London (40.6%). Four patients had IBD and were excluded, leaving 639 (57.9%) for inclusion. The age range was 25–90 years (median: 64 years, interquartile range

(IQR): 55–71) and 54.6% were male. The indications for colonoscopy reflected routine surveillance practice in these hospitals and were: adenoma surveillance in 312 (48.8%), of whom 66.3% were categorised as intermediate risk, 20.5% low risk, 13.2% high risk; genetic surveillance in 152 (23.8%) (including history of CRC (89) hereditary nonpolyposis colorectal cancer (19), familial adenomatous polyposis (16) and mis-match repair gene carriers (12)), other family history in 84 (13.1%); post-surgical CRC follow-up in 72 (11.3%) and other indications in 19 (3.0%).

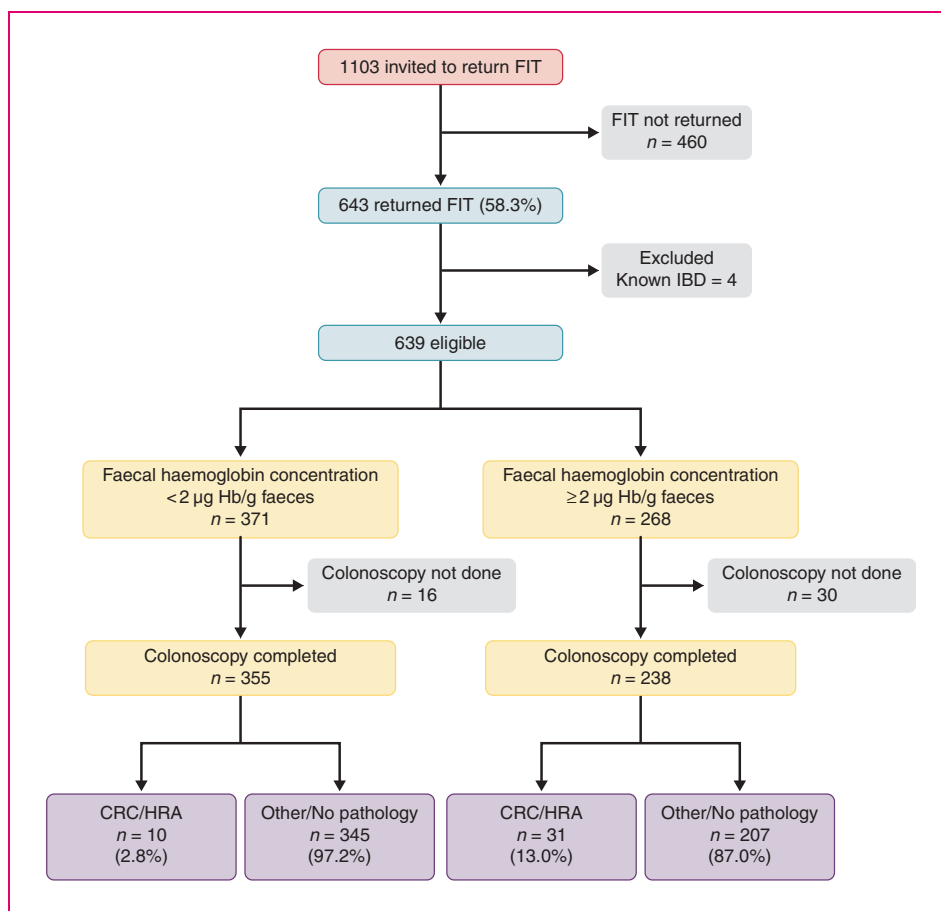
Of the 639 patients, 46 were excluded from analysis of FIT diagnostic performance; 19 patients did not respond to the colonoscopy appointment letter or cancelled their appointment, 8 did not attend, 3 patients were not fit for colonoscopy, 3 submitted a device that was unsuitable for analysis, 1 was cancelled, 1 underwent CT colonoscopy, 2 had an incomplete colonoscopy and 9 had not undertaken colonoscopy by the end of the study.

Of the 593 patients who had a f-Hb result and completed colonoscopy, advanced neoplasia was found in only 41 (6.9%); (4 CRC (0.7%)), 37 HRA (6.3%)).

## Diagnostic performance of FIT

For the detection of 41 cases of advanced neoplasia within the cohort of 593 patients, the performance of FIT was assessed at the LoD (2 µg Hb/g faeces) (Figure 1), LoQ (4 µg Hb/g faeces), and the lower limit of the usual working range (10 µg Hb/g faeces) for the assay. With a cut-off threshold for a positive test at 10 µg Hb/g faeces, 83.3% had a negative test (Table 1); at this threshold, 3/4 CRC and 17/37 HRA would have been missed. At the LoD threshold, 59.9% had a negative test; the yield of pathology at colonoscopy was doubled at 13.0% (31/238) but 2 of the 4 cancers and 8 of the 37 HRA would have been missed. Using the LoD as the cut-off for a positive test result increased the sensitivity for detection of CRC plus HRA from 51.2% to 75.6%, predominantly through increased detection of HRA, at the expense of a reduction in specificity. However, even at the LoD threshold, the sensitivity for CRC was only 50%; at this low threshold there was an associated small reduction in PPV due to the larger number of positive test results, whilst NPV was unchanged at around 99% due to the low prevalence of CRC in the study cohort (Table 2).

The prevalence of advanced neoplasia when grouped according to the main indications for surveillance was 8.2% in those under adenoma surveillance, 7.2% under CRC follow up, 6.1% in genetic surveillance, 3.7% in those with a family history and none of the five patients under surveillance for other clinical



**Figure 1.** Study flow diagram, depicting the yield of pathology using 2 µg Hb/g faeces (the LoD) as the cut-off for a positive test in a cohort of patients submitting a FIT test prior to scheduled surveillance colonoscopy.  
FIT: faecal immunochemical test; Hb: haemoglobin; LoD: limit of detection.

**Table 1.** The impact of using FIT cut-offs of LoD, LoQ, and conventional cut-off (<10 µg Hb/g faeces) on percentage of 'negative' tests and the prevalence of missed pathology at those thresholds in a cohort attending surveillance colonoscopy ( $n = 593$ ) (CRC, HRA, advanced neoplasia (CRC plus HRA) and LRA).

	<i>n</i>	%	<2 µg Hb/g faeces (LoD)		<4 µg Hb/g faeces (LoQ)		<10 µg Hb/g faeces	
			<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Colonoscopy diagnosis	593	100	355	59.9	429	72.3	494	83.3
CRC	4	0.7	2	0.6	3	0.7	3	0.6
HRA	37	6.2	8	2.3	9	2.1	17	3.4
CRC plus HRA	41	6.9	10	2.8	12	2.8	20	4.0
LRA	127	21.4	74	20.8	89	20.7	105	21.2

CRC: colorectal cancer; FIT: faecal immunochemical test; Hb: haemoglobin; HRA: higher-risk adenoma; LoD: limit of detection; LoQ, limit of quantitation; LRA: low-risk adenoma.

indications (Table 3). Assessment of performance of FIT at the LoD revealed some variation across the surveillance categories. Positivity ranged from 27.5% to 47.8%. The missed CRC were both within the CRC follow-up cohort, but the numbers in each subgroup are small, limiting the value of this analysis.

In summary, with the cut-off for a positive FIT result set at the LoD, almost 60% of surveillance patients in our study would have had undetectable f-Hb. An undetectable f-Hb was associated with a reduction in the overall risk of advanced neoplasia from 6.9% (in all-comers) to 2.8% (relative risk

**Table 2.** Faecal immunochemical test performance at the LoD, LoQ and conventional cut-off ( $<10 \mu\text{g Hb/g faeces}$ ) for CRC and HRA within a surveillance cohort ( $n = 593$ ) expressed as percentages (95% CI).

	$<2 \mu\text{g Hb/g faeces (LoD)}$	$<4 \mu\text{g Hb/g faeces (LoQ)}$	$<10 \mu\text{g Hb/g faeces}$
PPV			
CRC	0.8 (0.3–2.2)	0.6 (0.1–3.3)	1.0 (0.2–5.3)
HRA	12.2 (10.2–14.5)	17.1 (14.0–20.6)	20.2 (15.0–26.6)
CRC plus HRA	13.0 (10.9–15.5)	17.7 (14.4–21.5)	21.2 (15.8–27.9)
NPV			
CRC	99.4 (98.5–99.8)	99.3 (98.8–99.6)	99.4 (98.9–99.7)
HRA	97.7 (95.9–98.8)	97.9 (96.4–98.8)	96.6 (95.2–97.6)
CRC plus HRA	97.2 (95.3–98.3)	97.2 (95.6–98.3)	96.0 (94.5–97.0)
Sensitivity			
CRC	50.0 (6.8–93.2)	25.0 (0.6–80.6)	25.0 (0.6–80.6)
HRA	78.4 (61.8–90.2)	75.7 (58.8–88.2)	54.1 (36.9–70.5)
CRC + HRA	75.6 (59.7–87.6)	70.7 (54.5–83.9)	51.2 (35.1–67.1)
Specificity			
CRC	59.9 (55.9–63.9)	72.3 (68.5–75.9)	83.4 (80.1–86.3)
HRA	62.4 (58.2–66.5)	75.5 (71.8–79.1)	85.8 (82.6–88.6)
CRC plus HRA	62.5 (58.3–66.5)	75.5 (71.7–79.1)	85.9 (82.7–88.7)

CI: confidence interval; CRC: colorectal cancer; FIT: faecal immunochemical test; Hb: haemoglobin; HRA: higher-risk adenoma; LoD: limit of detection; LoQ, limit of quantitation; LRA: low-risk adenoma; NPV: negative predictive value; PPV: positive predictive value.

**Table 3.** Faecal immunochemical test performance at the LoD ( $2 \mu\text{g Hb/g faeces}$ ) for each of the four main indications for surveillance colonoscopy expressed as percentages (95% CI).

	Adenoma Surveillance ( $n = 292$ )	Genetics surveillance ( $n = 147$ )	Other family history ( $n = 80$ )	CRC follow up ( $n = 69$ )
CRC ( $n$ )	1	1	0	2
HRA ( $n$ )	23	8	3	3
CRC + HRA ( $n$ )	24	9	3	5
FIT test positive at LoD (%)	45.4	33.6	47.8	27.5
Missed pathology				
CRC	0	0	0	2
HRA	4	3	1	0
PPV				
CRC	0.8 (0.7–0.9)	1.1 (1.0–1.2)	N/A	0.0
HRA	14.4 (11.8–17.5)	5.3 (3.1–8.9)	9.1 (4.0–19.5)	9.1 (7.1–11.5)
CRC plus HRA	15.2 (12.4–18.3)	6.4 (4.1–9.9)	9.1 (4.0–19.5)	9.1 (4.5–17.6)
NPV				
CRC	100	100	N/A	94.4 (93.1–95.6)
HRA	97.6 (94.3–99.0)	93.6 (85.3–97.4)	98.3 (92.0–99.7)	100
CRC plus HRA	97.6 (94.3–99.0)	93.6 (85.3–97.4)	98.3 (92.0–99.7)	94.4 (85.0–98.1)
Sensitivity				
CRC	100 (2.5–100)	100 (2.5–100)	N/A	0.0 (0.0–84.2)
HRA	82.6 (61.2–95.1)	62.5 (24.5–91.5)	66.7 (9.4–99.2)	100
CRC plus HRA	83.3 (62.6–95.3)	66.7 (29.9–92.5)	66.7 (9.4–99.2)	60.0 (14.7–94.7)
Specificity				
CRC	55.9 (50.0–61.6)	33.6 (25.8–42.0)	N/A	50.7 (38.2–63.2)
HRA	58.9 (52.8–64.8)	33.1 (24.5–41.7)	74.0 (62.8–83.4)	54.5 (41.8–66.9)
CRC plus HRA	59.1 (53.1–65.0)	33.1 (25.4–42.1)	74.0 (62.8–83.4)	53.1 (40.2–65.7)

CI: confidence interval; CRC: colorectal cancer; FIT: faecal immunochemical test; Hb: haemoglobin; HRA: higher-risk adenoma; LoD: limit of detection; NPV: negative predictive value; PPV: positive predictive value.



reduction of 59.4%), and the risk of CRC from 0.7% (in all-comers) to 0.6% (relative risk reduction of 14%). On the other hand, a positive FIT was associated with an increase in prevalence of advanced neoplasia at colonoscopy from 6.9% (in all comers) to 13.0%.

## Discussion

We have studied FIT within the context of colonoscopy surveillance delivered in two NHS services, one in Scotland and the other in England. The yield of significant neoplasia within this surveillance cohort was very low (6.9%) and CRC accounted for only 0.7%. This is in keeping with a previously published landmark study.<sup>25</sup> With the cut-off for a positive FIT result set at the LoD, almost 60% of surveillance patients in our study had undetectable f-Hb. A positive FIT was associated with an increase in prevalence of advanced neoplasia at colonoscopy from 6.9% to 13.0%. An undetectable f-Hb was associated with a reduction in the overall risk of advanced neoplasia from 6.9% to 2.8% (relative risk reduction of 59.4%) and the risk of CRC from 0.7% to 0.6% (relative risk reduction of 14%). However, even at the LoD the sensitivity for CRC was only 50%.

Completing a FIT prior to surveillance colonoscopy proved feasible and acceptable to patients. The uptake in NHS Tayside was close to 70% but was considerably lower in London; it is not clear why this should be dissimilar, although the demographic characteristics of the populations differ considerably, and population-based bowel screening uptake in Greater London is similarly low at around 43% as compared with uptake in NHS Tayside, which was 59.9%, at the time of this study.<sup>26,27</sup>

A strength of this study is that the cohort of patients are representative of routine practice across the UK; a heterogeneous group at low, moderate and high risk of CRC and called for colonoscopy in accordance with the BSG surveillance guidelines. Patients were identified in date order from endoscopy surveillance registers, removing selection bias. Most patients under surveillance had a history of adenoma. This cohort continually accrues because of participation in the national bowel screening programmes. Approximately 30% of participants who have positive test results in the bowel screening programme are found to have an adenoma,<sup>28</sup> and most do accept entry to subsequent surveillance as a result. Patients under surveillance because of an underlying genetic risk of CRC were the second largest group. Under current guidelines, this group has the shortest surveillance interval of 2 years and therefore makes for the greatest demand for surveillance colonoscopy. The yield of advanced neoplasia was 6.5% in this group, which is slightly

higher than the 4.5% reported in a large Danish study of similar patients.<sup>29</sup> Patients with Lynch syndrome are at the highest risk of CRC, influenced by the type of genetic mutation carried, but, despite aggressive colonoscopy surveillance, interval CRC still arises, and debate over the most appropriate surveillance interval continues.<sup>30</sup>

A further strength of this study is that the performance characteristics of FIT were examined at low f-Hb, using the LoD and LoQ as potential cut-offs as well as the more usual 10 µg Hb/g faeces, as recommended for use in assessment of patients with symptoms in the National Institute for Health and Care Excellence (NICE) diagnostics guidance DG30.<sup>31</sup> Our rationale for this was that the detection of neoplasia should be the highest possible with current analytical methodology and technology. As shown in Table 1, lowering the cut-off from 10 µg Hb/g faeces to the LoD resulted in more cases of advanced neoplasia being detected, as expected. The sensitivity for detection of CRC + HRA increased predominantly through increased detection of HRA. However, no test is perfect; in those patients with an undetectable f-Hb below the LoD advanced neoplasia was present in 2.8%, of which CRC accounted for 0.6%. Although this equates to 50.0% of the CRC being missed, these figures must be viewed alongside the 0.6% miss rates for CRC at surveillance colonoscopy.<sup>9</sup>

A limitation of this study is that the low overall prevalence of advanced neoplasia makes it difficult to draw meaningful comparisons of FIT test performance by indication for surveillance. Others have studied subgroups of surveillance patients. Recently, a large study of patients enrolled in adenoma surveillance who were offered yearly FIT, and had their scheduled colonoscopy brought forward from 3 years if FIT was 'positive', reported that 41% of CRC and 67% adenoma would be missed if colonoscopy was replaced by f-Hb at a cut-off of 40 µg Hb/g faeces<sup>22</sup>; data using a cut-off of 10 µg Hb/g faeces were also considered, and, although a significant number of CRC and adenoma would have been missed, it should be noted that many patients at the low f-Hb cut-off did not undergo colonoscopy until 2 years after the FIT result. Others have reported that f-Hb is predictive of yield of advanced neoplasia at subsequent colonoscopy.<sup>32</sup> A recent study from Australia,<sup>33</sup> building on their previous work on the use of FIT in surveillance,<sup>34</sup> found that the risk of advanced neoplasia following a small adenoma was lower than that following an advanced adenoma, but was strongly predicted by a positive FIT result: it was concluded that reducing frequency of colonoscopy while providing annual FIT might be a more efficient use of resources. Recently, these authors suggested that, rather than omitting any colonoscopy, intervals

could be lengthened beyond 3 years in a personalised manner, dependent on f-Hb.<sup>35</sup>

The findings of our study are therefore of great significance. Using FIT in patients presently enrolled in colonoscopy surveillance programmes could assist clinicians in determining the underlying risk of advanced neoplasia and inform patients of the anticipated benefits of colonoscopy and associated risks of declining a colonoscopy. In the future, surveillance of patients at risk of CRC could take the form of regular FIT tests, following which patients could be counselled on their underlying risk of neoplasia based on the FIT result and individual risk profile, and surveillance colonoscopy could be tailored to individual requirements.

### Authorship

CM, JAS and RJCS designed, planned and conducted the study. CM and AH had overall responsibility for surveillance colonoscopy services and oversight of study recruitment. SC, PD and LG enrolled patients and assisted in data collection. JD performed the statistical analysis and produced the figures and tables. All authors contributed to data interpretation and writing of the paper. CM and CGF wrote the final draft, which was approved by all authors. CM accepts full responsibility for the conduct of this study. He had full access to all the data generated and had the final responsibility of the decision to submit for publication.

### Data

Data may be made available following discussion with Craig Mowat, corresponding author.

### Declaration of conflicting interests

CGF has undertaken consultancy with Kyowa-Medex Co., Ltd, Tokyo, Japan, and has received travel support from Alpha Labs Ltd, Eastleigh, UK. Other authors declare no competing interests.

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Chief Scientist Office (grant reference number CZH/4/1032). The funder of this study had no role in the design of the intervention, data collection, data analysis, data interpretation, or writing of the report.

### Ethics approval

This study was approved by NRES (National Research Ethics Service) – project 14/NS/0059 – on 4 April 2014. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.


### Informed consent


Formal patient consent was not required; instead, return of the FIT samples by participants constituted implied consent.

### Reporting guidelines

The STARD checklist ([equator-network.org/wp-content/uploads/2015/03/STARD-2015-checklist.pdf](http://equator-network.org/wp-content/uploads/2015/03/STARD-2015-checklist.pdf)) is documented as supplementary material

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### Supplemental material

Supplemental material for this article is available online.

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